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EXAMINER
RAO, MANJUNATH N

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/045,063	ALTENBUCHNER ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 16-27 are currently pending and are present for examination.

Applicants' amendments and arguments filed on 11-22-04, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically, Examiner has withdrawn all previously held rejections in view of cancellation of claims 9-15.

Examiner acknowledges the amendments to the 1st line of specification as well as description to figures 1 and 2 and updating of the sequence information.

Specification

The disclosure is objected to because of the following informalities: Applicants have provided the description for figure 2. However, the description does not match with the description provided with reference to figure 2 elsewhere in the specification. For example on page 13, a reference is made to figure 2 under the subtitle "Temperature stability" of the enzyme. However, the provided figure description does not make any reference to the temperature stability at all and instead indicates that it was standard activity assay. Appropriate correction is required or figure 2 needs to be cancelled.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 22 and claims 23-27 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 22 is drawn to a method of producing L-methionine by contacting the L-N carbamoylases with SEQ ID NO:2 encoded by SEQ ID NO:1 with N-carbamoyl-L-thienylalanine. It is not clear to the Examiner as to how this is possible. As applicants themselves admit in Table 1 that when N-carbamoyl-L-thienylalanine was provided as substrate to the above enzyme, the product that accumulated was L-Thienylalanine and it was only when the enzyme was contacted with N-carbamoyl-L-methionine that L-methionine accumulated as a product. Therefore claim 22 is rejected as indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing L-amino acids such as L-tryptophan, L-phenylalanine, and L-tyrosine by using the specific L-N-carbamoylase isolated from *Arthrobacter aurescens* having an amino acid sequence SEQ ID NO:2, encoded by the polynucleotide with SEQ ID NO:1, does not reasonably provide enablement for a method of producing any or all L-amino acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 16-21 are so broad as to encompass a method of producing any or L-amino acids using carbamoylase enzyme SEQ ID NO:2. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the method of producing any or all L-amino acids and with regard to extremely large number of carbamoylases broadly encompassed for use by the claims. With respect to the method of producing L-amino acids, the specification teaches that the substrate spectrum and the stereospecificity of the isolated rec-L-N-carbamoylase isolated from *A.aurescens* comprises of only few leading to the production of only 3 L-amino acids from a total of 20 naturally occurring L-amino acids. The specification does not teach a single universal method for producing any or all L-amino acids.

Furthermore, since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the use of only the nucleotide and encoded amino acid sequence of a single

carbamoylases with SEQ ID NO:2 capable of producing only three L-amino acids. It would require undue experimentation of the skilled artisan to make all or any L-amino acids using the polypeptide with SEQ ID NO:2. The specification is limited to teaching the use of SEQ ID NO:2 as a carbamoylase for producing only three L-amino acids but provides no guidance with regard to the making of all or any L-amino acids or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known and it is routine in the art to screen for multiple substitutions or multiple modifications or multiple sources, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass carbamoylases with SEQ ID NO:2 for making any or all L-amino acids because the specification does not establish: (A) a single universal method to produce any or all L-amino

acids using the above enzyme; (D)regions of the enzyme structure which may be modified without affecting its activity such that its activity can be altered to synthesize any or all L-amino acids; (E) the general tolerance of carbamoylases to modification and extent of such tolerance; (F) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (G) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method f making any or all L-amino acids, and the use of carbamoylases with an enormous number of amino acid modifications to SEQ ID NOS:2. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the enzymes for use in the above claimed method having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicants have traversed the above rejection. On the one hand applicants accept that the specification supports the production of "specific" amino acids such as L-tryptophan, L-tyrosine and L-phenylalanine, but on the other hand that these are ample examples for conversion of β-aryl-substituted L-amino acids. Applicants also point to Table 1 as support. However, as can be seen from Table 1, not all L-amino acids could be detected. Therefore, using their own evidence, Examiner reiterates that the specification does

not provide ample support for making any or all L-amino acids using the enzyme with SEQ ID NO:2. hence the above rejection is maintained.

Claims 22-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 22-27 are drawn to a method of making L-methionine using the carbamoylases enzyme with SEQ ID NO:2 by contacting the enzyme with N-carbamoyl-L-thienylalanine to produce L-methionine. However, the specification describes a method of making L-methionine by contacting the substrate N-carbamoyl-L-methionine but not N-carbamoyl-L-thienylalanine. The very same specification discloses the production of L-Thienylalanine using the substrate N-carbamoyl-L-thienylalanine and the above enzyme. Therefore, the specification is silent on any guidance or support for production of L-methionine using N-carbamoyl-L-thienylalanine which would lead those skilled in the art to undue experimentation. In order for the claims to be enabled it requires that one of ordinary skill in the art know or be provided with guidance for the same. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

Such guidance has not been provided in the instant specification. Hence the above rejection is maintained.

Conclusion

None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications

and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

February 9, 2005